We claim:

1. A method of treating or preventing chronic renal failure in a mammal, comprising conjointly administering to said mammal an OP/BMP morphogen and an Angiotensin-Converting Enzyme Inhibitor (ACEI).

2. A method of treating or preventing chronic renal failure in a mammal, comprising conjointly administering to said mammal an OP/BMP morphogen and an Angiotensin II Receptor Antagonist (AIIRA).

3. A method of treating or preventing chronic renal failure in a mammal, comprising conjointly administering to said mammal an inducer of endogenous OP/BMP morphogen expression and an Angiotensin-Converting Enzyme Inhibitor (ACEI).

4. A method of treating or preventing chronic renal failure in a mammal, comprising conjointly administering to said mammal an inducer of endogenous OP/BMP morphogen expression and an Angiotensin II Receptor Antagonist (AIIRA).

5. A method of treating or preventing chronic renal failure in a mammal, comprising conjointly administering to said mammal an agonist of an OP/BMP morphogen receptor and an Angiotensin-Converting Enzyme Inhibitor (ACEI).

6. A method of treating or preventing chronic renal failure in a mammal, comprising conjointly administering to said mammal an agonist of an OP/BMP morphogen receptor and an Angiotensin II Receptor Antagonist (AIIRA).

7. A method of treating or preventing chronic renal failure in a mammal, comprising introducing into the kidney of said mammal a therapeutically effective amount of renal mesenchymal progenitor cells pre-treated

conjointly with an ACEI and an agent that increases the abundance of an OP/BMP morphogen.

8. A method of treating or preventing chronic renal failure in a mammal, comprising introducing into the kidney of said mammal a therapeutically effective amount of renal mesenchymal progenitor cells pre-treated conjointly with an AIIRA and an agent that increases the abundance of an OP/BMP morphogen.

9. The method of claim 7 or 8, wherein the agent is an OP/BMP morphogen.

10. The method of claim 7 or 8, wherein the agent is an inducer of an OP/BMP morphogen.

11. The method of claim 7 or 8, wherein the agent is an agonist of an OP/BMP morphogen receptor.

12. A method for delaying the need for, or reducing the frequency of, chronic dialysis treatments, comprising conjointly administering to a mammal an OP/BMP morphogen and an ACEI.

13. A method for delaying the need for, or reducing the frequency of, chronic dialysis treatments, comprising conjointly administering to a mammal an OP/BMP morphogen and an AIIRA.

14. A method for delaying.the need for, or reducing the frequency of, chronic dialysis treatments, comprising conjointly administering to said mammal an inducer of endogenous OP/BMP morphogen expression and an ACEI.

15. A method for delaying the need for, or reducing the frequency of, chronic dialysis treatments, comprising conjointly administering to said mammal an inducer of endogenous OP/BMP morphogen expression and an AIIRA.

16. A method for delaying the need for, or reducing the frequency of, chronic dialysis treatments, comprising conjointly administering to said mammal an agonist of an OP/BMP morphogen receptor and an ACEI.

17. A method for delaying the need for, or reducing the frequency of, chronic dialysis treatments, comprising conjointly administering to said mammal an agonist of an OP/BMP morphogen receptor and an AIIRA.

18. A method as in any one of claims 1-17, wherein said mammal is afflicted with a condition selected from: chronic renal failure (CRF), end-stage renal disease (ESRD), chronic diabetic nephropathy, diabetic glomerulopathy, diabetic renal hypertrophy, hypertensive nephrosclerosis, hypertensive glomerulosclerosis, chronic glomerulonephritis, hereditary nephritis, or renal dysplasia.

19. A method as in any one of claims 1-17, wherein examination of a renal biopsy of said mammal indicates that said mammal is afflicted with a condition selected from: glomerular hypertrophy, tubular hypertrophy, glomerulosclerosis, or tubulo interstitial sclerosis.

20. A method as in any one of claims 1-17, wherein examination of said mammal indicates renal fibrosis.

21. The method of claim 20, wherein said examination is an ultrasound, NMR or CAT scan of said mammal.

22. A method as in any one of claims 1-17, wherein said mammal possesses a number of functional nephron units which is less than about 40% of a number of functional nephron units present in a mammal having intact healthy kidneys.

23. The method of claim 22, wherein said mammal possesses a number of functional nephron units which is less than about 20% of a number of functional nephron units present in a mammal having intact healthy kidneys.

24. The method of any one of claims 1-17, wherein said mammal is a kidney transplant recipient.

25. The method of any one of claims 1-17, wherein said mammal possesses only one kidney.

26. The method of any one of claims 1-17, wherein examination of a urinary sediment of said mammal indicates a presence of broad casts.

27. The method of any one of claims 1-17, wherein said mammal has a GFR which is chronically less than about 40% of a GFR_{exp} for said mammal.

28. The method of claim 27, wherein said mammal has a GFR which is chronically less than about 20% of a GFR_{exp} for said mammal.

29. The method of any one of claims 1-17, wherein said mammal is a human male weighing at least about 50 kg and has a GFR which is chronically less than about 40 ml/min.

30. The method of any one of claims 1-17, wherein said mammal is a human female weighing at least about 40 kg and has a GFR which is chronically less than about 30 ml/min.

31. The method of any one of claims 1-17, wherein said treatment or prevention reduces serum creatinine levels in said mammal by at least about 5% over 3 months.

32. The method of any one of claims 1-17, wherein prior to said treatment or prevention, said mammal presented a chronic decline in a clinical indicator of renal function, and after at least about 3 months of said treatment or prevention, said indicator stabilizes.

33. The method of any one of claims 1-6 and 12-17, wherein at least one of said ACEI, said AIIRA or said morphogen is administered orally, parenterally, intravenously, intraperitoneally, or into a renal capsule, or by an implanted device.

34. The method of claim 33, wherein a stent has been implanted into said mammal for said administration of at least one of said ACEI, said AIIRA or said morphogen.

35. The method of any one of claims 1-6 and 12-17, wherein at least one of said ACEI or said AIIRA, and at least one of said morphogen are conjointly administered at least once a week for a period of at least about one month.

36. The method of any one of claims 1-6 and 12-17, wherein at least one of said ACEI or AIIRA, and at least one of said morphogen are conjointly administered at least once a week for a period of at least about one year.

37. The method of any one of claims 1-6 and 12-17, wherein said ACEI or said AIIRA, and said morphogen are administered through different routes.

38. The method of any one of claims 1-6 and 12-17, wherein said ACEI or said AIIRA, and said morphogen are conjointly administered at different frequencies.

39. The method of any one of claims 1-6 and 12-17, wherein said morphogen is administered at a dosage of about 0.01-1000 μg/kg body weight of said mammal.

40. The method of claim 39, wherein said morphogen is administered at a dosage of about 10-300 μg/kg body weight of said mammal.

41. The method of any one of claims 1, 3, 5, 12, 14 and 16, wherein said ACEI is administered orally at a concentration of about 1-10,000 mg/L, preferably 10-1000 mg/L, 10-100 mg/L, 100-1000 mg/L, most preferably 100 mg/L.

42. The method of any one of claims 2, 4, 6, 13, 15 and 17, wherein said AIIRA is administered orally at a concentration of about 0.01-100 mg/kg body weight, preferably 0.1-10 mg/kg body weight, 0.2-5 mg/kg body weight, 0.5-2 mg/kg body weight, most preferably 1 mg/kg body weight.

43. The method of any one of claims 1-6 and 12-17, wherein said OP/BMP morphogen and, ACEI or AIIRA are administered in a single pharmaceutical composition.

44. The method of any one of claims 1-6 and 12-17, wherein said OP/BMP morphogen and, ACEI or AIIRA are administered in separate pharmaceutical compositions at or around the same time.

45. The method of any one of claims 1-6 and 12-17, wherein said OP/BMP morphogen and, ACEI or AIIRA are administered in separate pharmaceutical compositions at different times.

46. The method of any one of claims 1-17, wherein said morphogen (a) induces chondrogenesis in an ectopic bone assay; (b) prevents, inhibits, delays or alleviates loss of renal function in an animal model of chronic renal failure, or (c) causes a clinically significant improvement in a standard marker of renal function when administered to a mammal in, or at risk of, chronic renal failure.

47. The method of of any one of claims 1-17, wherein said morphogen comprises a polypeptide including at least a C-terminal cysteine domain of a protein selected from: a pro form, a mature form, or a soluble form of a polypeptide, wherein said polypeptide is: OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, or BMP9.

48. The method of claim 47, wherein said morphogen comprises a polypeptide including at least a C-terminal cysteine domain of a polypeptide selected from: a pro form, a mature form, or a soluble form of human OP-1.

49. The method of claim 1, wherein said morphogen comprises a polypeptide having at least 70% homology or 50% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

50. The method of claim 49, wherein said polypeptide has at least 75% homology or 60% identity with an amino acid sequence of a C-terminal. seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

51. The method of claim 49, wherein said polypeptide has at least 80% homology or 70% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

52. The method of claim 53, wherein said polypeptide has at least 90% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

53. The method of any one of claims 1, 3, 5, 7, 9-12, 14, and 16, wherein said ACEI is: any one compound of the formulas I-XXVIII or their salts thereof; acylmercapto and mercaptoalkanoyl prolines; captopril (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline); ether or thioether mercaptoacyl prolines; zofenopril; carboxyalkyl dipeptides; enalapril (N-(1-ethoxycarbonyl-3-phenylpropyl)-L-ananyl-L-proline); lisinopril; quinapril; ramipril; carboxyalkyl dipeptide mimics; cilazapril; benazapril; phosphinylalkanoyl prolines; fosinopril; trandolopril; phosphonamidate substituted amino or imino acids; phosphonate substituted amino or imino acids and salts thereof; ceronapril ((S)-1-[6-amino-2-[[hydroxyl(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline); BRL 36,378; MC-838; CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]-amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCL); CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid); Cetapril (alacepril, Dainippon); Ru 44570; Cilazapril; Ro 31-2201; Lisinopril; Indalapril (delapril); Rentiapril (fentiapril, Santen); Indolapril; Spirapril; Perindopril; Quinapril; CI 925 ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxy-carbonyl)-3-phenylpropyl]amino[-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCL); WY-44221; mercapto-containing compounds; pivopril; YS980; Omapatrilat; Alacepril;

moveltopril; quinaprilat; moexipril; perinodpril (S-9490); pentopril; ancovenin; phenacein; or nicotianamin.

54. The method of any one of claims 2, 4, 6, 8-11, 13, 15, and 17, wherein said AIIRA is: Losartan (Cozaar®), Valsartan (Diovan®), Irbesartan (Avapro®), Candesartan (Atacand®), Telmisartan (Micardis®), tasosartan, zolarsartan, Teveten (eprosartan mesylate) or olmesartan medoxomil (Benicar).

55. The method of any one of claims 1, 3, 5, 7, 9-12, 14, and 16, wherein said ACEI is Enalapril.

56. A pharmaceutical composition comprising a therapeutically effective amount an ACE inhibitor and an OP/BMP morphogen formulated with pharmaceutically acceptable salt, carrier, excipient or diluent.

57. A pharmaceutical composition comprising a therapeutically effective amount an AIIRA and an OP/BMP morphogen formulated with pharmaceutically acceptable salt, carrier, excipient or diluent.

58. The pharmaceutical composition of claim 56, wherein the ACE inhibitor is Enalapril.

59. The pharmaceutical composition of claim 57, wherein the AIIRA is: Losartan (Cozaar®), Valsartan (Diovan®), Irbesartan (Avapro®), Candesartan (Atacand®), Telmisartan (Micardis®), tasosartan, zolarsartan, Teveten (eprosartan mesylate) or olmesartan medoxomil (Benicar).

60. The pharmaceutical composition of claim 56 or 57, wherein the morphogen is the polypeptide of SEQ ID NO: 3.

61. The pharmaceutical composition of claim 56 or 57, wherein the morphogen is a first polypeptide including at least a C-terminal cysteine domain of a protein selected from: a pro form, a mature form, or a soluble form of a second polypeptide, wherein said second polypeptide is: OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, or BMP9.

62. The pharmaceutical composition of claim 56 or 57, wherein said morphogen comprises a polypeptide having at least 70% homology or 50% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

63. The pharmaceutical composition of claim 62, wherein said polypeptide has at least 75% homology or 60% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

64. The pharmaceutical composition of claim 62, wherein said polypeptide has at least 80% homology or 70% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

65. The pharmaceutical composition of claim 62, wherein said polypeptide has at least 90% identity with an amino acid sequence of a C-terminal seven-cysteine domain of human OP-1 (SEQ ID NO: 2).

66. The pharmaceutical composition of claim 56, wherein said ACEI is: any one compound of the formulas I-XXVIII or their salts thereof; acylmercapto and mercaptoalkanoyl prolines; captopril (1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline); ether or thioether mercaptoacyl prolines; zofenopril; carboxyalkyl dipeptides; enalapril (N-(1-ethoxycarbonyl-3-phenylpropyl)-L-ananyl-L-proline); lisinopril; quinapril; ramipril; carboxyalkyl dipeptide mimics; cilazapril; benazapril; phosphinylalkanoyl prolines; fosinopril; trandolopril; phosphonamidate substituted amino or imino acids; phosphonate substituted amino or imino acids and salts thereof; ceronapril ((S)-1-[6-amino-2-[[hydroxyl(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline); BRL 36,378; MC-838; CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]-amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCL); CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid); Cetapril (alacepril, Dainippon); Ru 44570; Cilazapril; Ro 31-2201; Lisinopril; Indalapril (delapril); Rentiapril (fentiapril, Santen); Indolapril; Spirapril; Perindopril; Quinapril; CI 925 ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-

(ethoxy-carbonyl)-3-phenylpropyl]amino[-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCL); WY-44221; mercapto-containing compounds; pivopril; YS980; Omapatrilat; Alacepril; moveltopril; quinaprilat; moexipril; perinodpril (S-9490); pentopril; ancovenin; phenacein; or nicotianamin.

67. The pharmaceutical composition of claim 57, wherein said AIIRA is: Losartan (Cozaar®), Valsartan (Diovan®), Irbesartan (Avapro®), Candesartan (Atacand®), Telmisartan (Micardis®), tasosartan, zolarsartan, Teveten (eprosartan mesylate) or olmesartan medoxomil (Benicar).

68. A package pharmaceutical comprising the pharmaceutical composition of any one of claims 56-67, in association with instructions for administering the composition to a mammal for treatment or prevention of chronic renal failure.

Abstract

The present invention provides reagents and methods for the treatment, and pharmaceuticals for use in the prevention and/or treatment, of chronic renal failure and other renal disorders in subjects (particularly mammalian subjects) renal replacement therapy. The methods involve the conjoint administration of ACE (Angiotensin-Converting Enzyme) inhibitors or Angiotensin II Receptor Antagonists (AIIRAs) with one or more OP/BMP family of proteins (morphogens, or inducers of morphogens, or agonists of the corresponding morphogen receptors, etc.). The invention also provides methods for implantation of renal cells induced with the conjoint administration of ACE inhibitors or AIIRAs with those morphogens.